Chapter 4

Immunosenescence and Senescence Immunosurveillance: One of the Possible Links Explaining the Cancer Incidence in Ageing Population

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Additional information is available at the end of the chapter

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1. Introduction

Since the discovery of cellular senescence significant advances were made to understand its molecular determinants and its physiological role in biological processes such as cancer and aging [1]. Recently, an intimate and complex relationship between senescent cells and the immune system has been highlighted [2]. In addition to their role in senescence immunosurveillance, immune cells display altered functions with age. This process is known as immunosenescence. Although immunosenescence is a slightly different mechanism than cellular senescence, it shares some similarities. This review article briefly describes features, markers, triggers and molecular regulators of cellular senescence and focuses on its role during cancer development. We then introduce immunosenescence and highlight what might be its consequences in cancer development. Finally, taking into account that senescence immunosurveillance is crucial for tumor eradication [2], we provide several hypotheses to explain what could be the impact of immunosenescence on senescence immunosurveillance in a specific cancer context.

2. Cellular senescence

2.1. Historical discovery of cellular senescence

Senescence comes from the Latin word *senex* meaning old age. It was observed approximately half a century ago by Leonard Hayflick while cultivating primary human fibroblast [3, 4]. He observed that primary cells proliferate in culture for approximately 55 population doublings before reaching the "Hayflick limit" which marks the end of their proliferative capacity and

the entry into an irreversible growth arrest state. He proposed a theory "that the finite lifetime of diploid cells strains *in vitro* may be an expression of ageing or senescence at the cellular level". Since, the term "replicative senescence" has been used to designate this type of cellular senescence but, as we will see, senescence can also be induced in a replicative independent manner in response to various cellular insults. Senescence is not limited to human primary fibroblast as it has been observed in various primary cells [5-8] including immune cells [9] and also takes place in other species such as Mouse [10], Rat [11], Chicken [12], Caenorhabditis elegans [13], Zebrafish [14] and Yeast [15].

2.2. Features of cellular senescence

2.2.1. Morphology

Senescent cells lose their original morphology. Larger than their normal counterparts, they also have a much larger flattened cytoplasm that contain many vacuoles and cytoplasmic filaments [16, 17], a bigger nucleus and nucleoli and are sometimes multinucleated [18, 19]. In some cases, senescent cells display an increase in the number of lysosomes and golgi [20-24].

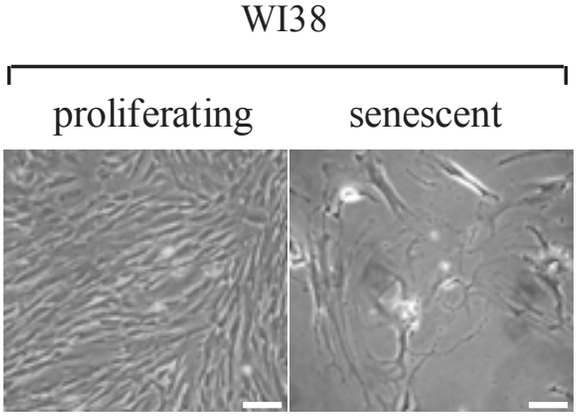

Figure 1. Morphology analysis of primary human fibroblasts (proliferating versus senescent).

2.2.2. Growth arrest

One of the most obvious features of cellular senescence is growth arrest. Indeed, cells are usually blocked in the G1 phase of the cell cycle [25] and in some cases they display (4n) DNA suggesting that cells are either blocked in the late S, G2 or M phases [26, 27]. Cell cycle progression is regulated by cyclin dependent kinases (CDKs) that bind to cyclins [28]. These complexes are regulated by cyclin dependent kinase inhibitors (CKIs) which are essential for the establishment of the senescent growth arrest state [29]. CKIs are divided into two families. The CIP (CDK-interacting protein) and KIP (cyclin-dependent kinase inhibitor protein) [30] and the INK4, for inhibitors of CDK4 [31]. CDK-cyclin complexes favour G1 cell cycle progression by phosphorylating RB family members [32]. RB family proteins are transcriptional

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co-factors that interact with and inhibit E2F transcription factors activity required for DNA synthesis. Upon the phosphorylation of RB family members by the CDK-type D and E cyclin complexes, E2F transcription factors are released from their interaction with RB proteins leading to cell cycle progression [33] (Figure 2). The CDK4/6-type D cyclins complexes interact with KIP/CIP inhibitors. However, during cellular senescence, INK4 proteins increase and inhibit CDK4/6-cyclin D formation [32]. This enables the activation of RB family members and the inhibition of E2F transcription factors. Additionally, the bioavailability of KIP and CIP proteins increases and they no longer interact with CDK4/6/Cyclin D complexes. It allows them to interact and inhibit CDK2-type E or A cyclin complexes (Figure 2).

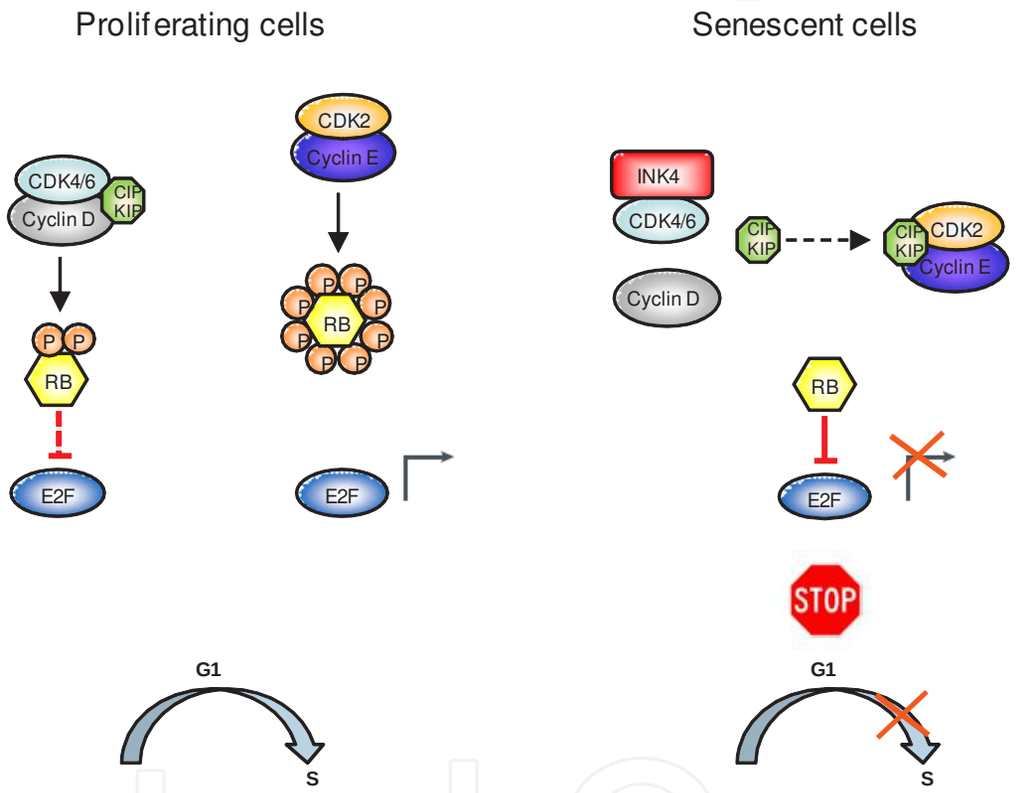

Figure 2. Cell cycle arrest (G1 phase) associated with cellular senescence.

In proliferating cells the CKI levels are low, the CDK/cyclin complexes are functional and RB family members are found hyperphosphorylated leading the E2F family members' activation and G1 progression. In senescent cells, the levels of CKI increase, CDK/Cyclin complexes are inhibited and RB family members are active leading to E2F transcription factors inhibition and G1 cell cycle arrest.

2.2.3. Altered gene expression

Senescent cells also display a specific gene expression signature. A notable example are senescence-associated-secretory-phenotype (SASP) molecules such as interleukin 6 (IL-6), interleukin 8 (IL-8), plasminogen activator inhibitor 1 (PAI-1), insulin growth factor binding

protein 7 (IGBP7), (ECM) degradation enzymes such as collagenase and metalloprotease (MMPs) but also CKIs, CIP and KIP as previously mentioned [34]. Some genes are also found down-regulated during cellular senescence. It is the case for polycomb complex members such as enhancer of zeste homolog 2 (EZH2) and chromobox homolog 7 (CBX7) [5, 35].

2.2.4. Senescence markers

Several markers have been used to specifically identify senescent cells. In addition to an altered cell morphology, growth arrest state and a specific gene expression signature, senescent cells are associated with an increased β-galactosidase activity, detectable at pH 6.0 and known as "senescence-associated-beta-galactosidase (SA-βgal) activity" [36] (Figure 3).

Figure 3. Senescence-associated-beta-galactosidase (SA-βgal) activity detectable at pH6 and yelling a blue colour in senescent cells. Primary human fibroblasts were used for the analysis.

At a chromatin level, specific facultative heterochromatin structures associated with senescent cells were discovered and termed senescence-associated-heterochromatin-foci (SAHF) [37]. These structures regulated by the Retinoblastoma gene (RB) are involved in E2F target genes repression and maintain the cell cycle arrest. They contain markers of heterochromatin such as hypo-acetylated histones, methylated histones (H3K9Me) and the presence of heterochromatin protein 1 (HP1). The histone variant macroH2A, and HMGA a non histone protein, have been identified as crucial regulators in SAHF formation [38] (Figure 4).

2.3. Replicative senescence

Although replicative senescence was first observed in 1961, it took more than 30 years to gain insights into the molecular regulators underlying this process. We now know that it is largely due to telomere lengths and structures. Telomeres are protective structures that cap the end of all eukaryotic chromosomes. They are long double stranded DNA sequences composed of TTAGGG repeats, oriented 5′-to-3′ towards the end of the chromosome (Figure 5) [39]. Telomeres contain a complex composed of six proteins known as the shelterin complex. It comprises telomeric repeat binding factor 1 (TRF1), telomeric repeat binding factor 2 (TRF2), transcriptional repressor/activator protein (RAP1), TRF1-interacting nuclear factor 2 (TIN2),

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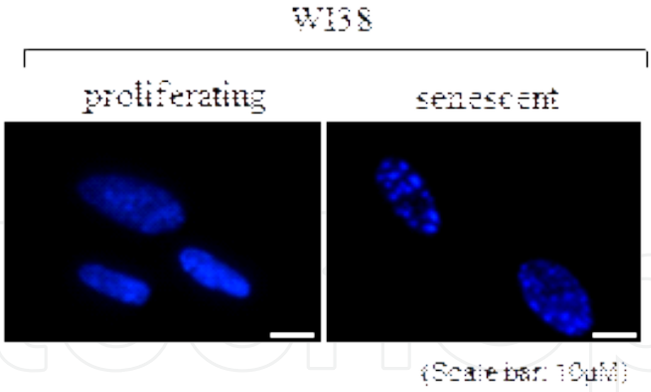

Figure 4. Senescence-associated-heterochromatin-foci (SAHF) of normal and senescent primary human fibroblasts. Dots representing SAHF are visible in senescent cells.

TIN2-interacting protein (TPP1) and protection of telomeres 1 (POT1) (Figure 5). The last two components, TPP1 and POT1 regulate the access of the telomeric substrate for the telomerase [40]. Telomere lengths are maintained by telomerase, a ribonucleoprotein complex that includes a RNA template (known as TERC) and the reverse transcriptase catalytic subunit (TERT) (Figure 5) [40]. Telomerase activity is mainly dictated by the TERT expression, as TERC seems to be ubiquitously transcribed [41]. In 1990, it was noticed that the telomeres length decreased during serially passage human primary fibroblasts and it was suggested that telomere size might be responsible for replicative senescence [42]. Eight years later, it was functionally demonstrated that re-introducing telomerase expression in normal primary cells led to elongated telomeres, lifespan extension and abrogation of replicative senescence [43, 44]. Since then, telomerase re-expression alone [45] or in combination with other alterations [46] has been associated with the immortalisation of various human cells types. Although telomere size is a critical trigger for replicative senescence, telomere structure is also a main determinant [47, 48]. In conclusion, dysfunctional telomeres both short or with an altered structure trigger replicative senescence.

2.4. Premature senescence

2.4.1. Oncogene-induced senescence (OIS)

In 1997, it was observed that in response to an oncogenic form of Ras (H-Ras^{G12V}) primary cells entered a premature senescence state [50]. Oncogene-induced senescence (OIS) is not restricted to Ras but can be extended to most of the MAPK pathway actors (Raf, Mek) and other oncogenic pathways. In accordance, the loss of bona fide tumour suppressors genes that restrain the activity of oncogenic pathways, such as phosphatase and tensin homolog (PTEN), Retinoblastoma (Rb), von Hippel-Lindau tumor suppressor (VHL) and neurofibromin 1 (NF1), has also been associated with premature senescence [10]. OIS is suggested to be a replicative senescence independent mechanism as cells expressing the catalytic subunit of the telomerase (TERT) still undergo OIS [51]. Whereas senescence in ageing tissues had been observed since 1995 [36], the

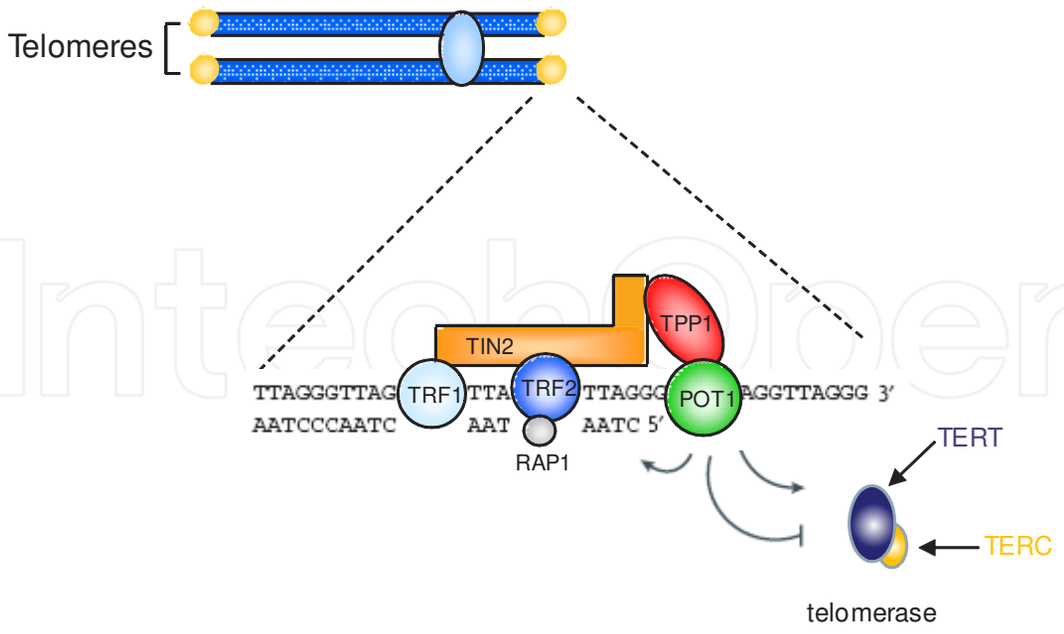

Figure 5. The telomeres and the telomerase. Telomeres, TTAGGG repeats, oriented 5' to 3' towards the end of the chromosome are regulated by six proteins that make up the shelterin complex. The telomeres lengths are maintained by the telomerase, a ribonucleoprotein complex composed of a RNA template (TERC) and the reverse transcriptase catalytic subunit (TERT). Adapted from [49].

demonstration of OIS in a physiological setting was demonstrated ten years later using various mouse model expressing a hyper-active oncogene form or a deleted tumor suppressor [10].

2.4.2. Oncogene-inactivation-induced senescence (OIIS)

Cellular senescence is not limited to primary cells but can also be triggered in cancer cells [52]. Cancer cells develop oncogene addiction, a term to describe a cell dependence on an oncogenic pathway to maintain its tumoral properties [53]. Various groups have been trying to identify these oncogene addictions using synthetic lethal screening [53, 54]. Interestingly, targeting oncogene addiction can result in cellular senescence. For example the inhibition of CDK4, a cyclin dependant kinase involved in cell cycle progression, in K-Ras^{G12V} driven non small cell lung carcinoma is associated with cellular senescence induction [55]. Moreover, the inhibition of several embryonic factors known to exert oncogenic properties (T-box 2 (TBX2), twist homolog 1/2 (TWIST 1/2)) can also result in cellular senescence [56, 57]. Finally c-Myc inhibition, a bHLH-LZ transcription factor involved in several tumoral processes such as proliferation, angiogenesis and cell metabolism [58], can leads to senescence induction in cancer cell lines and also in c-Myc transgenic driven lymphomas or osteosarcomas mouse models [59].

2.4.3. Stress-induced premature senescence (SIPS)

Stresses are major determinants of cellular senescence [21]. Even if replicative senescence, OIS and OIIS can also generate similar stresses and could be classified in the stress-induced cellular senescence category, we decided to write a specific section for SIPS. Oxygen is one of the major

determinants of stress-induced-premature-senescence (SIPS). Oxygen singlet (O_2) is not toxic for cells however O_2 consumption leads to reactive oxygen species (ROS) [21]. ROS can be classified into two groups. The first group which includes reactive species such as superoxide and hydroxyl radicals is composed of molecules with free radical containing one or more unpaired electrons in their outer molecular orbitals. The second group which includes hydrogen peroxide, ozone, peroxinitrate and hydroxide is composed of non-radical ROS that remain chemically reactive and can be converted to radical ROS [60].

Evidences demonstrating that ROS can trigger cellular senescence are now common. For example, cultivating primary human cells in 3% O_2 levels which is closer to the physiological conditions (normal physiological conditions vary from 1-2% in some parts of the brain, skin, heart and kidney to 14% in the lungs) [61], allowed cells to undergo 20 supplemental populations doublings before reaching replicative senescence [62]. Conversely, raising the oxygen levels over 20% or exposing cells to sublethal doses of ROS such as H_20_2 led to a premature senescence like state [63, 64].

SIPS is not restrained to oxidative stress. It can be induced in response to additional inadequate culturing conditions such as abnormal growth factors, the absence of neighbour cells and extracellular matrix components and inadequate concentrations of nutrients, [45, 65, 66]. Other physical, chemical and cellular stressors such as mitomycin C and ionizing radiation can also trigger SIPS [67].

2.5. Pathways regulating cellular senescence

2.5.1. The INK4B/ARF/INK4A

The INK4B/ARF/INK4A locus encodes three tumour suppressor genes that play critical regulatory roles in cellular senescence [31]. Two of these tumour suppressors, $p15^{INK4B}$ and $p16^{INK4A}$, are cyclin dependent kinase inhibitors (CKIs) that trigger cell cycle arrest by inhibiting CDK4 and CDK6 complexes [34]. ARF, the third gene encoded by the locus, is a critical regulator of the p53 tumour suppressor pathway [68]. ARF and $p16^{INK4A}$ share common exons but are encoded in alternative reading frames leading to the production of unique proteins [31].

Polycomb repressive group complexes (PRCs) play a crucial role in the regulation of the locus [69]. The polycomb family is composed of two repressive complexes PRC1 and PRC2. PRC2 establishes the repressive mark leading to the recruitment of the maintenance polycomb complex PRC1. Various polycomb proteins such as CBX7, CBX8, TBX2, TBX3 and Bmi1 have been functionally implicated in the repression of cellular senescence by inhibiting the INK4B/ARF/INK4A locus [5, 70-72]. To counteract the repressive action of the polycomb complexes, several mechanism are activated during cellular senescence. These include the removal or inhibition of polycomb complexes by MAPKAP [73], by the chromatin remodeling SWI/SNF complex [74] and/or the activation of the INK4B/ARF/INK4A locus by JMJD3 [75, 76] (Figure 6).

Additional regulators of the locus include the stress activated p38MAPKinase. Activated in response to various stresses such as high levels of ROS, dysfunctional telomeres and OIS, it regulates cellular senescence in various contexts [77]. It can activate $p16^{INK4A}$, $p15^{INK4B}$ and ARF

[78]. Although the locus products are mainly regulated by epigenetic mechanism, post-translational modifications can also play a role in their regulation. For example, ARF stability is regulated by the E3 ubiquitin ligase TRIP12/ULF [68] and TGF-β stabilises $p15^{INK4B}$ [79]. $p16^{INKA4}$ is activated in response to UV treatment through the inhibition of a SKP2 related degradation [80].

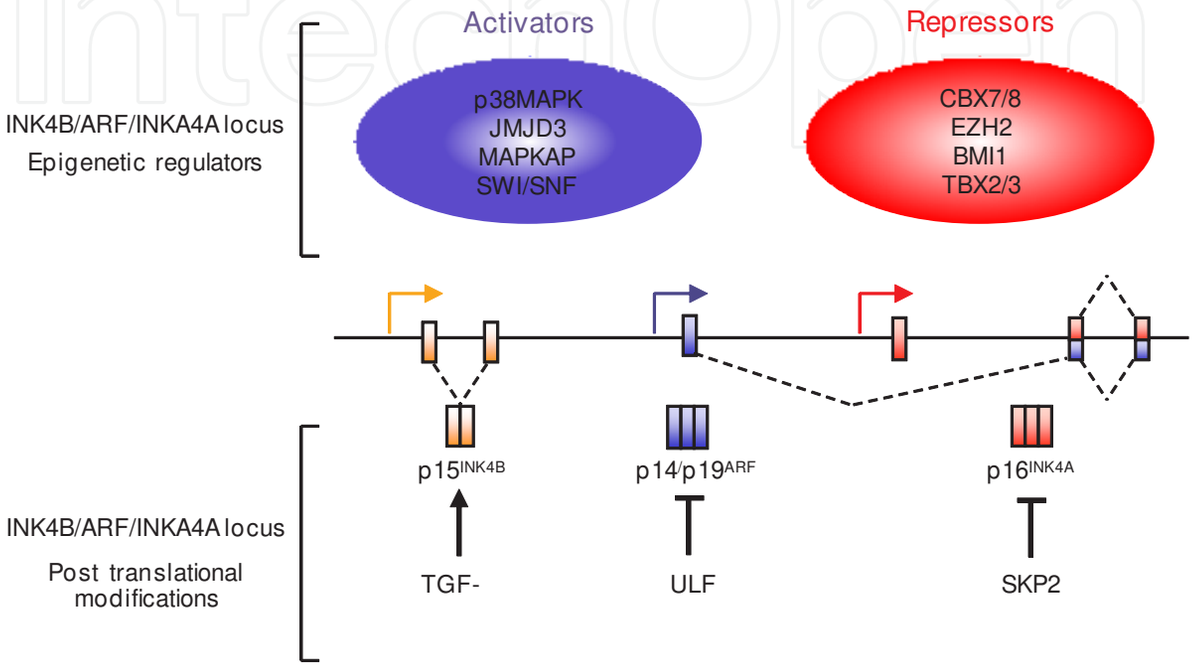

Figure 6. The INK4B/ARF/INK4A locus in cellular senescence.

The locus is mostly regulated by epigenetic mechanism. It involves repressors such as the polycomb proteins (CBX7/8, EZH2, BMI1 and TBX2/3) and activators including histone demethylases (JMJD3), protein kinases (p38MAPK, MAPKAP) and chromatin remodeling complexes (SWI/SNF). Post translational modifications also regulate the locus products.

2.5.2. The DNA damage/p53 pathway

Activated in response to stimuli that trigger a DDR such as dysfunctional telomeres, OIS, ionising radiation and ROS, the p53 pathway is critical in the regulation of senescence [81] (Figure 7).

The activation of a DNA damage response consists in the recruitment of DNA damage sensors at the sites of damage. Various DNA damage sites associated with cellular senescence have been described. These include telomere-dysfunction-induced-foci (TIFs) [82], senescence-associated DNA damage foci (SDF) [83] and DNA segments with chromatin alterations reinforcing senescence (DNA-SCARS) [84].

The DNA damage pathway is activated following the activation of two large protein kinases ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR). Once recruited at the DNA damage sites, they phosphorylate and activate the histone variant H2AX [85]. The molecular events involved in single stranded breaks (SSBs) and double stranded breaks (DSBs) then differ and will not be described herein. The activation of the DDR kinases cascade, involving DNA damage mediators and diffusible kinases, results in the phosphorylation and activation of p53 which in turn activates $p21^{CIP1}$, one of its transcriptional targets to regulate growth arrest and cellular senescence [81]. The functional role of DDR in cellular senescence has been demonstrated using various functional approaches. Inactivating DDR proteins as well as p53 and its transcriptional target $p21^{CIP1}$ is sufficient to abrogate cellular senescence in various settings [81]. The p53 pathway can also be activated in a DDR independent mechanism. For example, ARF plays a crucial role in the activation of p53. Activated in response to oncogenic stimulations, it activates p53 by sequestering the E3 ubiquitin protein ligase mouse double minute 2 (MDM2 or HDM2 in humans), an inhibitor of p53 [86] (Figure 7).

The DNA damage/p53 pathway is activated in response to dysfunctional telomeres, oncogenic or oxidative stress, ionizing radiations and cytotoxic drugs. A DNA damage response (DDR) is elicited leading to the activation of local apical kinases, DNA-damage mediators, diffusible kinases and ultimately p53 and $p21^{CIP1}$. The p53 pathway can also be activated by ARF following an oncogenic stress. Adapted from [81].

2.5.3. Reactive oxygen species (ROS)

ROS are critical regulators of OIS [87]. In accordance, ROS regulated proteins such as seladin-1 (modulators of peroxiredoxines, a class of antioxidants) have also been involved in OIS [88]. Enzymes that generate ROS such as 5-lipooxygenase (5LO) mediate Ras induced senescence [89]. ROS are not only involved in Ras induced senescence. Akt was recently identified as a major determinant of various types of cellular senescence by modulating oxygen consumption and down-regulating ROS scavengers [90]. ROS can also mediate replicative senescence. For example, large amount of ROS produced by dysfunctional mitochondria can modulate telomere length and replicative senescence [91]. In accordance, antioxidant proteins can negatively regulate cellular senescence. The extracellular superoxide dismutase (SOD) increases the lifespan of primary cells [92] and over-expressing the antioxidant enzyme catalase to the mitochondria increase mice lifespan [93].

2.5.4. Small non coding RNAs

miRNAs are small (approximately 23 nucleotides) RNAs that play a crucial role in gene regulation [94]. miRNAs bind 3'UTR and sometimes 5'UTR of the mRNA to modulate their translation and/or stability. The regulatory role of miRNAs during cellular senescence has recently been addressed [95]. Expression profiling studies indicate an altered expression among various miRNAs during cellular senescence [95]. Functionally, several miRNAs have been identified as repressor [96] or activators of cellular senescence [97] in normal but also cancer cells [98].

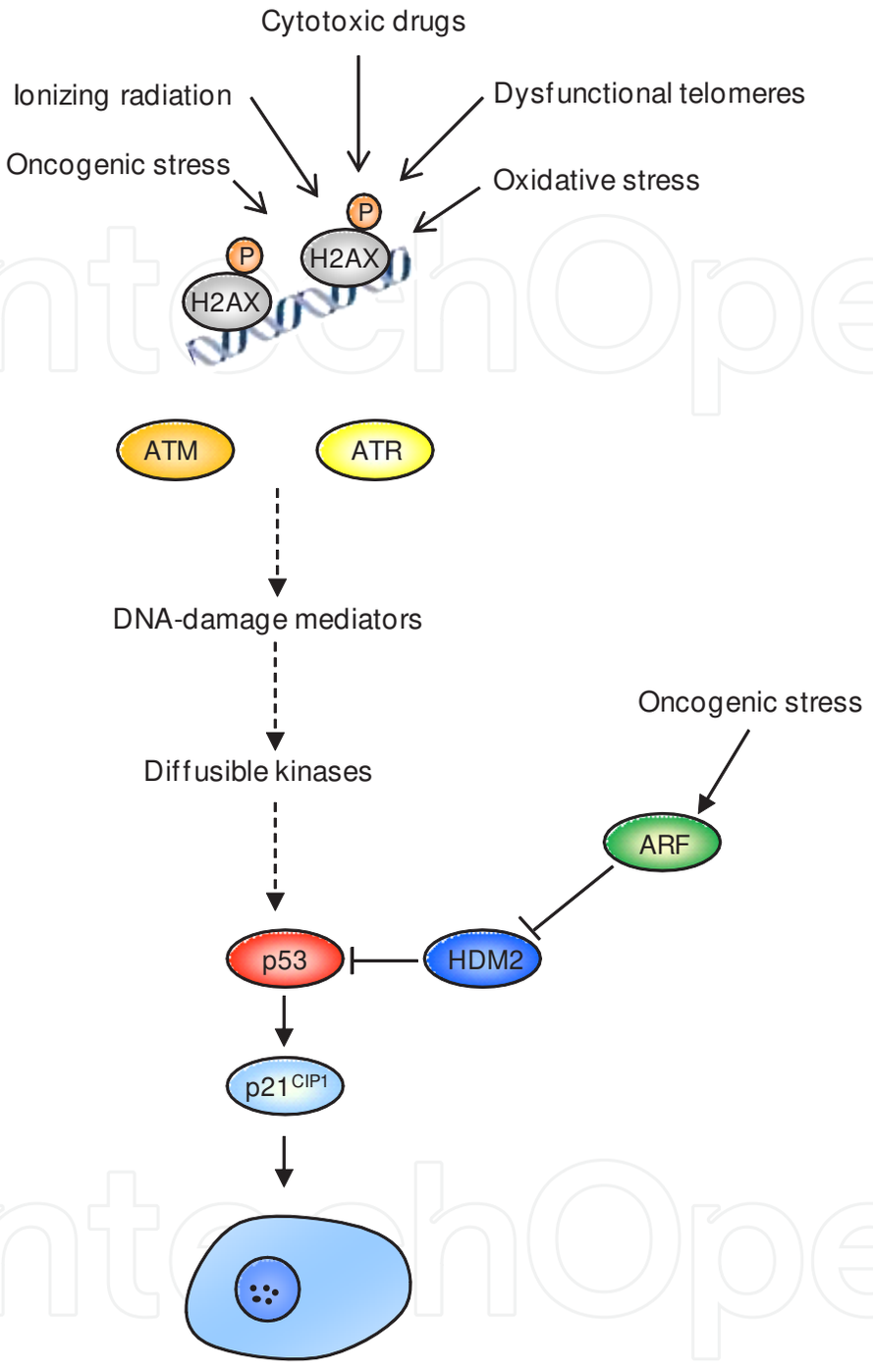

Figure 7. The DNA damage/p53 pathway in cellular senescence.

2.5.5. The autophagic pathway

Autophagy is a recycling process mediated by autophagosomes, which are double membrane vesicules that engulf cytoplasmic contents and then fuse and deliver their content to lysosomes. Lysosomes contain hydrolases that digest the material which ultimately leads to a breakdown of the vesicules and their constituents [99].

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Senescent cells display an increase in autophagic vacuoles, a gradual shift from the proteasome pathway to autophagy for polyubiquitinated protein degradation [100] and an upregulation of autophagy regulators such as the ATG related genes (ULK1 and ULK3) [101]. Modulating critical components of the autophagic process can regulate cellular senescence. Inhibition of ATG proteins (ATG-5 and ATG-7) is sufficient to induce an escape from cellular senescence [101]. Conversely, over-expressing ATG target genes such as of ULK3 reduces cell growth [101].

2.6. Cellular senescence and cancer: The tumour point of view

Ever since the discovery and the term replicative senescence introduced by Hayflick in 1965 [3], it has been proposed that senescence can block tumour progression. Primary normal cells are said to be "mortal", and in contrast, cancer cell lines are immortal. Therefore, an escape from replicative senescence is a critical stage that has to be overcome during tumour progression. To physiologically demonstrate this hypothesis, mouse models knockout for the RNA component of the telomerase ($TERC^{-/-}$) were used. The replicative senescence triggered in response to dysfunctional telomeres in these mice was shown to limit tumour progression and lead to tumour regression [102, 103]. In accordance with these results, late generation $TERC^{-/-}$ deficient mice have been shown to be resistant to multistage skin carcinogenesis [104] and are more resistant to tumour formation in a subset of cancer mouse models [105, 106]. Oncogene-induced senescence (OIS) has also been identified as a failsafe program *in vivo,* and this, in response to a physiological aberrant oncogenic activation [10]. Additional inactivation of tumour suppressor genes regulating cellular senescence leads to progression towards malignant stages and full blown tumours [10]. In accordance, premalignant tumour display high levels of senescence whereas it is absent in later stages of tumorigenesis [10]. Finally, cellular senescence is not only a barrier against early stages of tumor progression. It can be reactivated in established tumors leading to tumor eradication [52].

In response to various cellular stresses such as dysfunctional telomeres, oncogene activation, oxidative stress and cytotoxic stresses normal cells acquire various alterations. Cellular senescence is activated to restrain neoplastic expansion. The inactivation of critical tumor suppressor genes (p53, $p16^{INK4}$, ARF…) leads to cellular senescence escape and progression towards more aggressive tumors. Cellular senescence can be reactivated in tumors in response to the activation of tumor suppressors or oncogene inhibition. This reactivation leads to tumor regression [52].

3. Immunosenescence

3.1. Features of immunosenescence

Cellular senescence can also be detected in immune cells [107]. Immunosenescence is a slightly different process than cellular senescence. Indeed, immunosenescence refers to cellular hypoproliferation in response to mitogenic or antigen stimulation and is often observed in ageing immune cells. In contrast, cellular senescence is associated with a permanent cell cycle arrest underlined with specific molecular markers. Immunosenescence affects both adaptative

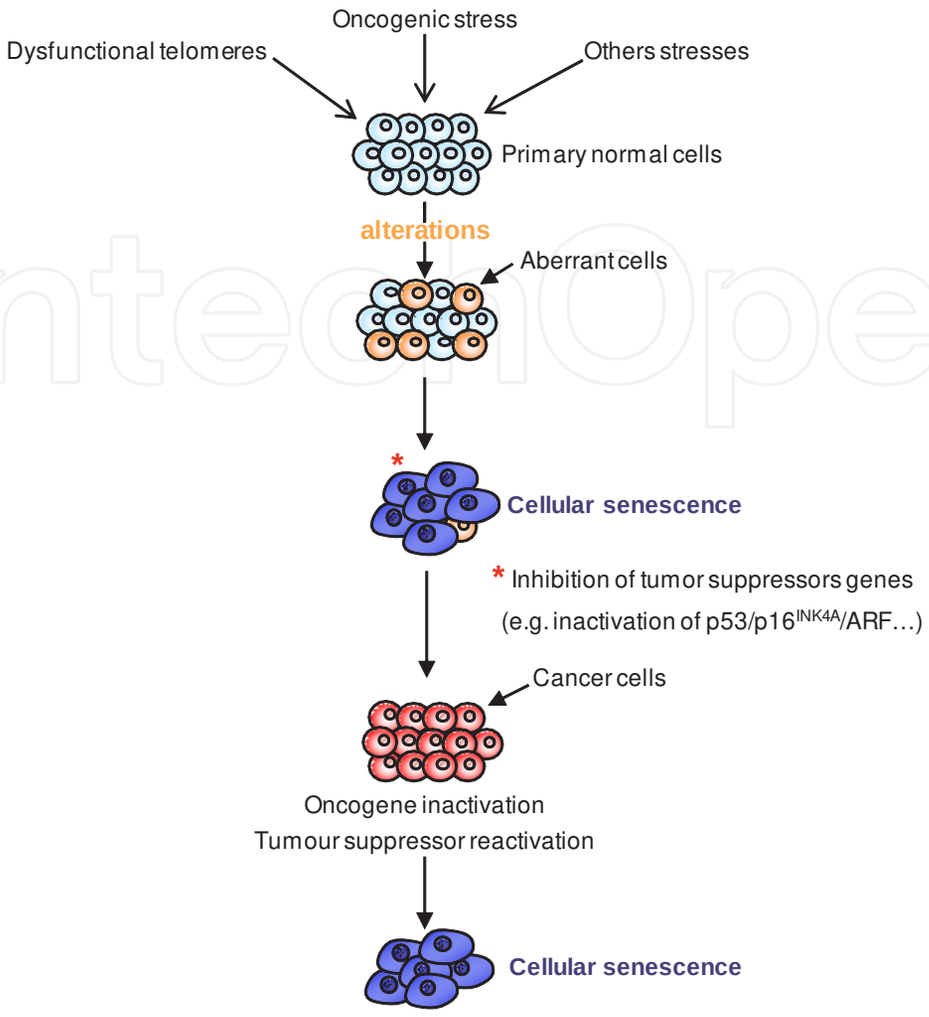

Figure 8. Cellular senescence acts as a tumor suppressive mechanism.

(T and B Lymphocytes) and innate immune cells (Natural killer cells (NK), Natural killer T cells (NKT), Macrophages, Neutrophils, Monocytes and Dendritic cells) [108, 109]. To date, the molecular determinants of immunosenescence have not been very well described. However, similarities with senescence in non immune cells are found. For example, immunosenescence of T cells is regulated by $p16^{INK4A}$ and $p21^{CIP1}$ [110, 111]. Differentiated T cells have shorter telomeres and an inactive telomerase [107]. Functionally, the ectopic telomerase expression maintains telomere size and delays immunosenescence [107]. However, immunosenescence also differs from cellular senescence. For example, inhibiting TNF-α receptor 1 partially reverses T cell immunosenescence in what is suggested to be a caspase-3 dependent mechanism [112]. Specific immunosenescence markers also exist. For example, cell surface markers such as CD27 and CD28 are lost in differentiated senescent CD4+ and CD8+ T cells and the killer cell lectin-like receptor subfamily G member 1 (KLRG1) is also known as a cell surface marker of immunosenescence [107]. Premature immunosenescence has not been characterized so far but one might expect that similar mechanism could be involved in premature senescence and premature immunosenescence. It could be interesting to assess whether stresses such as

high ROS levels, chemical or physical cellular stressors can trigger premature senescence. Additionally, it would be interesting to determine if the autophagic pathway and miRNAs are also implicated in various immunosenescence settings.

3.2. The triggers of immunosenescence

Various factors could explain immunosenescence. Thymic involution might play a role. It consists of shrinkage of the thymus with age and results in a decrease output of naïve T lymphocytes [113]. Altered immune signaling also seems to play a role. For example, in the elderly, the composition of lipid rafts is altered and this is associated with a decreased activity of some signaling pathways [114]. Above all, chronic antigen stimulation (e.g. chronic infections, tumor antigens) is the major trigger of immunosenescence. Cytomegalovirus (CMV) but also Epstein-Barr Virus (EBV) infection, to a lesser extent, are determinants of immunosenescence [115]. In accordance, the number of CD8+ cells expressing T cell receptor (TCR) specific CMV antigens in the ageing population increases. This has no effect in the number of T cell in the periphery however the expansion of CMV specific T cells results in a decrease in T cell repertoire [115]. In innate immune cells, an alteration of various receptors activity (e.g. Toll like receptor (TLR)) and in the number of some circulating innate immune cells seem to favor innate immunosenescence [109].

3.3. The consequences of immunosenescence

Immunosenescence is associated with decreased immune functions [109]. Neutrophils, the first innate immune cell to be at the site of pathogen entry, display a decreased chemotaxis and in free radical production and a decreased intracellular killing. Monocytes and macrophages both exhibit a decreased in phagocytosis and NK cells a decreased cytotoxicity. Dendritic cells display decreased phagocytosis, chemotaxis but also a reduced ability to activate the adaptative immune cells via antigen presentation [109]. Additionally to not being efficiently activated by the innate immune cells, adaptative immune cells are also affected by immunosenescence (particularly the T cell compartment). An inhibition of interleukine-2 (IL-2) production, increased DNA damage, telomere shortening but also a decrease in the number of naïve T cell (both CD4+ and CD8+) and an increase in the number of memory T cell leading to a weaker immunosurveillance are observed [115].

4. Immunosenescence and cancer

4.1. Tumors evade the immune system

Escape from immunosurveillance is now considered a cancer hallmark [116]. Immunosurveillance is a term used to define how immune cells identify and destroy abnormal antigen upon recognition [117]. This immunological process required for clearing tumors is often altered during cancer progression giving place to cancer favoring processes such as immunoselection, immunosubversion and ultimately immunosuppression [115, 117]. During cancer develop-

ment, a complex crosstalk between the tumor and the immune microenvironment takes place. Premalignant tumors send stress signals to the immune cells activating both innate and adaptative responses. In this context of immunosurveillance, the immune response is highly functional and eliminates surrounding tumors. However, tumor cells activate various mechanisms that allow immunosurveillance escape. These include the secretion of various cytokines, mechanisms to induce T cell apoptosis, anergy of naïve T cells, the activation of myeloid suppressor cells, the physical interaction of tumor cells with T cells, the suppression of NKT cell activities and downregulation of cell surface markers [115]. Immunosurveillance escape leads to a state of "equilibrium" between the tumor and the immune system, a process known as immunoselection. It is named as such because aggressive tumor cells that are capable of co-existing or suppressing the immune system are selected [115]. These cells eventually increase in number and secrete various immunosuppressive molecules (e.g. prostaglandin E2 (PGE2), nitric oxides) [117]. The immune system is therefore critical in suppressing tumor growth and its alteration is required from tumor progression. Interestingly, virtually of all the immune cells involved in immunosurveillance are known to be altered with age [115].

4.2. Cancer arises with age: A role for immunosenescence?

Cancer is a pathology associated with age [118]. Indeed, cancer incidence and prevalence increase with age suggesting an important relationship between the two biological processes [118]. During life, an organism is doomed to accumulate mutations favoring cancer development. The triggers of such mutations include environmental factors such as carcinogens, UV lights, viruses and free radicals among others [116]. On the other hand, cancer can no longer be regarded as a cell autonomous process. Recent advances demonstrate that the microenvironment plays a crucial role in modulating cancer development [116]. Although the role of the immune system in cancer development in ageing population is currently uncertain, it is clear that the immune system is altered with age [115]. As previously mentioned, the immune system is critical for clearing tumors, at least in early stages of tumorigenesis. Additionally, we have seen that immunosenescence is associated with profound immune alterations leading to a decrease in various immune cells activity. The activation of the adaptative immune response by dendritics cells is crucial for the activation of T-cell. Interestingly in the elders, immunosenescence of dendritics cells which impacts various co-receptors leads to a weakened T cell response [115]. The alteration of TLRs could also favor cancer development in ageing populations. Indeed, TLRs are crucial in the activation of innate immune cells. Their alterations leads to a decreased phagocytosis of innate immune cells and renders them less capable of destroying tumors. Ageing populations also have an increase amount of immune suppressive cells such as T regulatory cells that inhibit innate immune cells activity though direct cell-cell interaction. Myeloid derived suppressor cells (MDSC) are composed of a heterogeneous population of innate immune cells that can suppress the activation of CD4+ and CD8+ T cells. Interestingly, MDSC are activated by various anti-inflammatory signals (e.g IL-10, TGF-β) that are found increased in the elderly. Additionally, IDO, an immunosuppressive molecule that inhibits T cells responses, is also found up-regulated in ageing populations. Changes in the immune system that could favor cancer development are not limited to the innate immune cells. With ageing there is a gradual shift of Th1 towards Th2 in the T cells repertoire and this

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leads to an alteration in the activity of both naïve and cytotoxic lymphocytes. In summary, various immunosuppressive mechanisms are found up-regulated in the elderly [115]. Considering the crucial role of the immune system in cancer eradication, it suggests that immunosenescence could play a role in cancers associated with age.

5. Immunosenescence and senescence immunosurveillance

5.1. Senescence immunosurveillance

An intimate relationship between cellular senescence and the immune system has recently been identified [2]. Using various mouse models, it was demonstrated that the reactivation of p53 in established tumours was associated with cellular senescence and tumour regression [119, 120]. However, as senescent cells do not die of apoptosis and can persist in some tissue for many years [121], the fate of senescent cells remained uncertain especially in a cancer context. Since the discovery of a secretory phenotype associated with cellular senescence (SASP), it has been suggested that senescent cells can initiate cross-talks with the microenvironment [2]. It was therefore hypothesised that senescent cells could be cleared by the immune system. In accordance, it was demonstrated in a mouse model of liver carcinoma that the activation of an innate immune response (NK cells macrophage and neutrophils) was responsible for the clearance of senescent tumours [120]. In liver cancer, senescence immunosurveillance thus seems to be required to clear senescent tumors. Interestingly, senescence immunosurveillance is not limited to liver cancer as it was also required for the complete remission of lymphoma and leukemia mouse models [122]. In these models, the adaptative immune response and more specifically CD4+ T cells were necessary for tumour eradication and also for senescence induction suggesting a complex interplay between senescent cells and the immune system [2]. Such interplay has been tackled in a mouse model of lymphomagenesis [123]. In a model of OIS *in viv*o resulting in apoptosis, macrophage were attracted and required to engulf apoptotic reminders. Both cellular senescence and apoptosis were shown to act together via the innate immune response to inhibit tumour progression. In turn, activated macrophages secreted various cytokines such as TGF-β to induce cellular senescence of malignant cells [123]. These results clearly demonstrate a crucial role of immunosurveillance in clearing senescent tumors and amplifying senescence induction. To reinforce the role of senescence immunosurveillance as a barrier against cancer, the inactivation of CD4+ T cell following OIS of hepatocytes in mice led to tumor progression [124].The role CD4+ T cell in preventing tumor progression in this mouse model was dependent upon the activation of monocytes and macrophages [124]. What is surprising is that the inhibition of cellular senescence did not activate the immune system suggesting that during cancer development a functional senescence response might be required for an efficient immunosurveillance and tumor suppression [125]. It is therefore tempting to suggest that cellular senescence plays a significant role during immunosuppression [126]. It will also be interesting to demonstrate if senescence immunosurveillance also takes place in other organs during cancer development and whether it is involved in tumor suppression.

5.2. Defects in senescence immunosurveillance: A role for immunosenescence?

It appears that a functional immune system is required for efficient senescence clearance and tumor suppression. As immunosenescence affects normal immune homeostasis and senescent cells increase with age [118], it is tempting to speculate that in the elderly a defect in senescence immunosurveillance could contribute to the increased cancer incidence. In line with this hypothesis is the fact that all the immune cells involved in senescence immunosurveillance seem to be altered with age. However, to date no functional experiments have been carried to test such hypothesis. Mouse models of ageing recapitulating immunosenescence in which cellular senescence is induced could be of great interest to determine this possibility.

6. Conclusion

Immunosenescence is a field that holds great promises. To date, some of the molecular determinants of immunosenescence are still to be discovered. Identifying such mechanism could shed light on this cellular process and might help us to find ways to counteract such mechanism. Additionally, assessing the role of immunosenescence during cancer development in ageing population and more specifically its role during senescence immunosurveillance in the elderly could shed light on the mechanism associated with cancer.

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